



INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

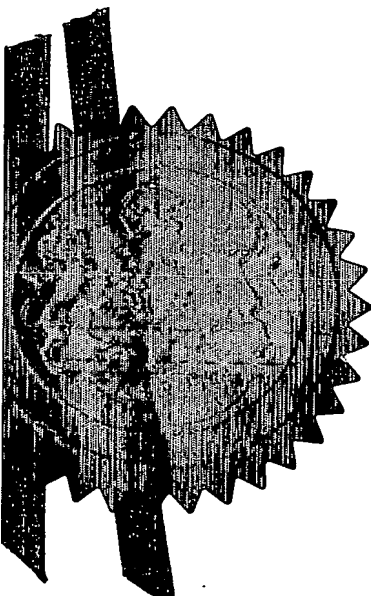
In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed *Andrew Gersey*
Dated 10 January 2005

BEST AVAILABLE COPY



Patents Form 1/77

Patents Act 1977
(Rule 16)

THE PATENT OFFICE
SN
23 DEC 2003
RECEIVED BY FAX



23DEC03 0861488-1 003022
P01/7700 0.00-0329716.5 ACCOUNT CHA

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference

PZ03102

2. Patent application number

(The Patent Office will fill this part in)

0329716.5

3. Full name, address and postcode of the or of each applicant (underline all surnames)

AMERSHAM PLC
Amersham Place
Little Chalfont
Buckinghamshire HP7 9NA

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

8189375004
United Kingdom

23 DEC 2003

4. Title of the invention

RADICAL TRAP

5. Name of your agent (if you have one)

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

ROLLINS, Anthony, John; HAMMER, Catriona, MacLeod;
HAMMETT, Audrey, Grace, Campbell and BRYAN, Ian, Bennett
Amersham plc
Amersham Place
Little Chalfont
Buckinghamshire HP7 9NA

Patents ADP number (if you know it)

8189375004

6. Priority. Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months.

Country

Priority application number
(if you know it)

Date of filing
(day / month / year)

7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note d)

Number of earlier UK application

Date of filing
(day / month / year)

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request?

Yes

Answer YES if:

- a) any applicant named in part 3 is not an inventor, or
- b) there is an inventor who is not named as an applicant, or
- c) any named applicant is a corporate body.

Otherwise answer NO (See note d)

Patents Form 1/77

0089853 23-Dec-03 02:43

Patents Form 1/77

9. Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheets of this form

Description	22
Claim(s)	5
Abstract	1
Drawing(s)	0

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for a preliminary examination and search (Patents Form 9/77) 1

Request for a substantive examination (Patents Form 10/77)

Any other documents (please specify)

11. I/We request the grant of a patent on the basis of this application.

Signature(s) ROLLINS, Anthony. John

A. J. Rollins

Date 23 December 2003

12. Name, daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

BANNAN, Sally
01494 542023
sally.bannan@amersham.com

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

- If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.
- Write your answers in capital letters using black ink or you may type them.
- If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
- If you have answered YES in part 8, a Patents Form 7/77 will need to be filed.
- Once you have filled in the form you must remember to sign and date it.
- Part 7 should only be completed when a divisional application is being made under section 15(4), or when an application is being made under section 8(3), 12(6) or 37(4) following an entitlement dispute. By completing part 7 you are requesting that this application takes the same filing date as an earlier UK application. If you want the new application to have the same priority date(s) as the earlier UK application, you should also complete part 6 with the priority details.

DUPLICATE

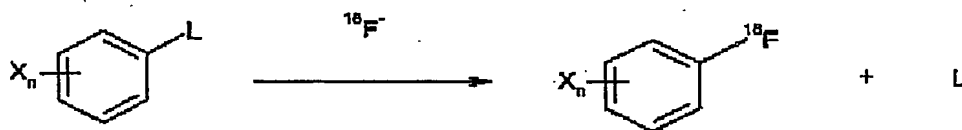
Radical Trap

Technical Field of the Invention

The present invention relates to the field of radiochemistry and in particular to radiofluoridation. Specifically, the invention relates to a novel method for the radiofluoridation of iodonium salts wherein a free radical trap is included in the reaction mixture. An additional embodiment of the invention is the radiofluoridation of iodonium salts using a solid phase reaction.

Description of Related Art

Aromatic nucleophilic substitution using the [^{18}F] fluoride anion to displace a suitable leaving group from an electron deficient aromatic ring is known as a method for the production of [^{18}F] fluoroarenes. The nucleophilic substitution reaction is illustrated below:



wherein X_n represents between 2 and 4 electron withdrawing groups and L represents a suitable leaving group, e.g. fluoro, bromo, nitro, tertiary amino or iodo.

The radiochemistry is performed using a nucleophilic radiofluorinating agent such as [^{18}F] caesium fluoride or [^{18}F] potassium fluoride. Preferably, a phase transfer reagent such as KryptofixTM is used when the radiofluorinating agent is [^{18}F] potassium fluoride. These radiofluorinating agents are prepared from cyclotron-produced no carrier added (NCA) [^{18}F] fluoride [as described by Aigbirhio *et al* 1995 J Fluorine Chem 70 p279].

The use of this reaction in the radiofluoridation of iodonium salts has been reported by Pike *et al* [1995 J Chem Soc Chem Comm pp2215-16] although with variable radiochemical yield (RCY). The reason for the variability in RCY was not understood. Subsequent reports from the same group [Shah *et al* 1998 J Chem Soc (Perkin Trans 1) pp2043-6 and Martin-Santamaría *et al* 2000 Chem Comm pp649-50] do not offer any further explanation for the variable RCY. More recently, Wüst *et al* [2001 J Labelled

€

Cpd Radiopharm 44 pS12-3] reported that the reaction of phenyliodonium tosylate with [^{18}F] potassium fluoride (in the presence of KryptofixTM) yielded a very low amount of the desired [^{18}F] corticosteroid. Furthermore, the present applicants have found that radiofluoridation of iodonium salts according to the methods described above produces highly variable RCY (<5% to 40%) of the desired [^{18}F] aryl fluoride product. Such lack of reproducibility makes the use of iodonium salts for the synthesis of [^{18}F] aryl fluorides problematic.

Summary of the Invention

Decomposition of iodonium salts by a free radical process has been identified as a significant factor in the observed yield variability of fluoridation reactions using said iodonium salts. Accordingly, the inclusion of a free radical trap in the reaction mixture blocks the radical chain decomposition pathway for iodonium salts such that only the reaction leading to fluoridation can occur and the yield of aryl fluoride becomes high and reproducible. The reaction may also be carried out on solid phase. In both the solution and the solid phase the preferred method of the present invention is radiofluoridation.

Detailed Description of the Invention

In a first aspect, the present invention relates to a method for the production of an aromatic fluorine-labelled compound comprising fluoridation of an iodonium salt with a fluoride ion source characterised in that the reaction mixture contains a free radical trap.

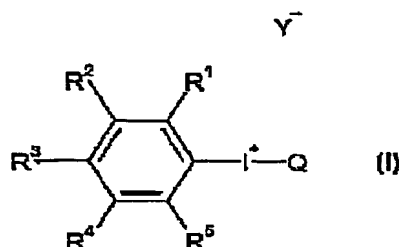
The "fluoride ion source" of the present invention is suitably selected from potassium fluoride, caesium fluoride and tetraalkylammonium fluoride. The preferred fluoride ion source of the invention is potassium fluoride which is most preferably activated with a phase transfer reagent, e.g. KryptofixTM.

The term "free radical trap" is defined as any agent that interacts with free radicals and inactivates them. A suitable free radical trap of the invention is selected from 2,2,6,6-Tetramethylpiperidine-N-Oxyl (TEMPO), ascorbate, para-amino benzoic acid (PABA), α -tocopherol, hydroquinone, di-t-butyl phenol, β -carotene and gentisic acid. Preferred free radical traps of the invention are TEMPO, di-t-butyl phenol, ascorbate and PABA, with TEMPO being most preferred. Suitable quantities of the free radical trap in the

3

reaction mixture are 10-300 Mol%, with 60-150 Mol% being preferred and 90-110 Mol% being most preferred.

The term "iodonium salt" is defined in the present invention as a compound comprising an ion of the form Y_2I^+ . Preferably, the iodonium salt of the invention is of Formula I:



wherein:

Q is a precursor of the fluorine-labelled compound of the invention;

R^1 - R^5 are independently selected from hydrogen, nitro, cyano, halogen, C_{1-10} hydroxyalkyl, C_{2-10} carboxyalkyl, C_{1-10} alkyl, C_{2-10} alkoxyalkyl, C_{1-10} hydroxyalkyl, C_{1-10} aminoalkyl, C_{1-10} haloalkyl, C_{6-14} aryl, C_{3-12} heteroaryl, C_{3-20} alkylaryl, C_{5-12} arylene, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} acyl, C_{7-10} aroyl, C_{2-10} carboalkoxy, C_{2-10} carbamoyl, C_{2-10} carbamyl, or C_{1-10} alkylsulphinyl, or protected versions of any of these groups; or alternatively forms a four- to six-membered ring together with the R group to which it is adjacent, or protected versions thereof; and,

Y^- is an anion selected from triflate, nonaflate, mesylate and hexaflate.

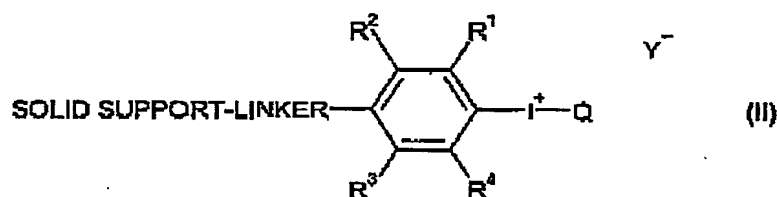
"Alkyl" used either alone or as part of another group is defined herein as any straight, branched or cyclic, saturated or unsaturated C_nH_{2n+1} group, wherein unless otherwise specified n is an integer between 1 and 6.

"Aryl" used either alone or as part of another group is defined herein as any C_{6-14} molecular fragment or group which is derived from a monocyclic or polycyclic aromatic hydrocarbon, or a monocyclic or polycyclic heteroaromatic hydrocarbon.

The term "halogen" means a group selected from fluorine, chlorine, bromine, and iodine, including isotopes thereof.

Suitable protection for R^1 to R^5 may be achieved using standard methods of protecting group chemistry. After the fluoridation is complete, any protecting groups may be removed by simple procedures which are also standard in the art. Suitable protection and deprotection methodologies may be found, for example, in Protecting Groups in Organic Synthesis, Theodora W. Greene and Peter G. M. Wuts, published by John Wiley & Sons Inc.

The iodonium salt of the invention is preferably solid support-bound as in Formula II:



wherein

Q is a precursor of the fluorine-labelled compound; and,

R^1 - R^4 and Y^- are as defined above for Formula I.

In the compound of Formula II, the "solid support" may be any suitable solid-phase support which is insoluble in any solvents to be used in the process but to which the linker can be covalently bound. Examples of suitable solid support include polymers such as polystyrene (which may be block grafted, for example with polyethylene glycol), polyacrylamide, or polypropylene or glass or silicon coated with such a polymer. The solid support may be in the form of small discrete particles such as beads or pins, or as a coating on the inner surface of a cartridge or on a microfabricated vessel.

In the compound of Formula II the "linker" may be any suitable organic group which serves to space the reactive site sufficiently from the solid support structure so as to maximise reactivity. Suitably, the linker comprises zero to four aryl groups and/or C_{1-20} alkyl, C_{2-20} alkoxyalkyl or C_{1-20} haloalkyl, and optionally one or more additional substituents such as oxygen, halogen, amide or sulphonamide. The linker may also suitably be a polyethylene glycol (PEG) linker. Examples of such linkers are well known to those skilled in the art of solid-phase chemistry.

23 December 2003

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

THE PATENT OFFICE
SN
23 DEC 2003
RECEIVED BY FAX

• • •
• • • Amersham

Amersham plc
Amersham Place
Little Chalfont
Buckinghamshire
HP7 9NA, UK

T +44 (0) 1494 542040

F +44 (0) 1494 542996

Email tony.rollins@amersham.com

BY FAX AND SPECIAL DELIVERY
TOTAL FAX PAGES: 33

Our Ref: PZ03102

Deposit A/C No: D03022

Dear Sirs/Madam,

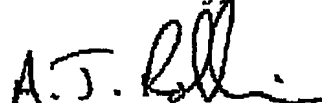
Re: New Patent Application
Applicant: Amersham plc
Title: 'Radical Trap'

We are enclosing the undermentioned documents:

Patent Forms: Request for Grant 1/77
Request for Preliminary Examination & Search 9/77
Fee Sheet
2 copies of the specification

We would ask you to debit our account No. D03022 for any fees that are payable for this application.

Yours faithfully,



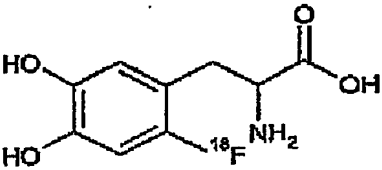
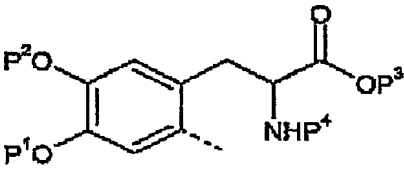
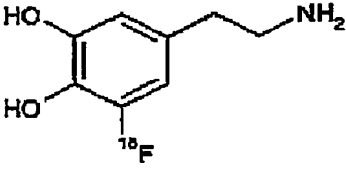
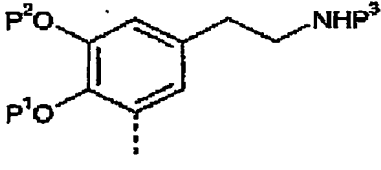
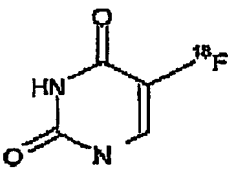
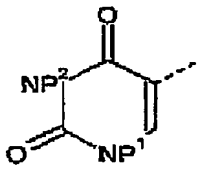
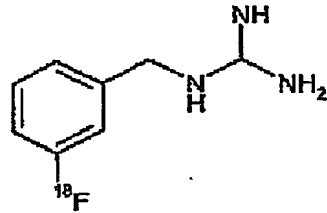
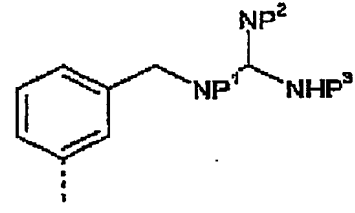
Anthony J Rollins
Agent for the Applicant

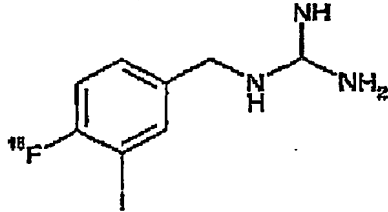
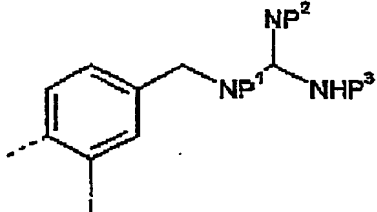
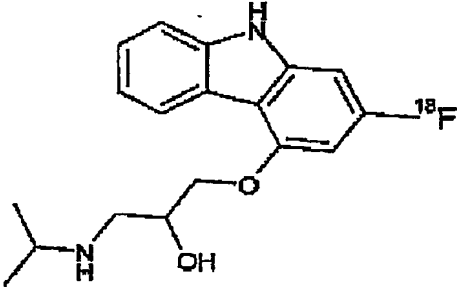
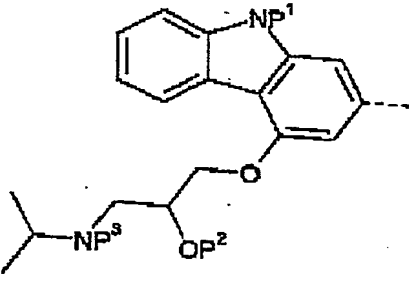
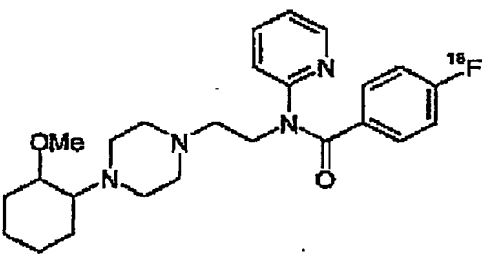
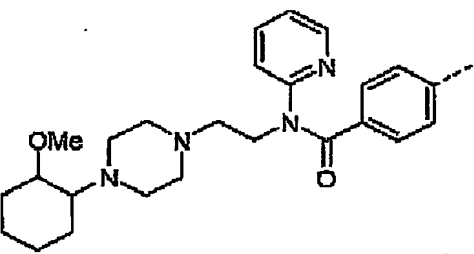
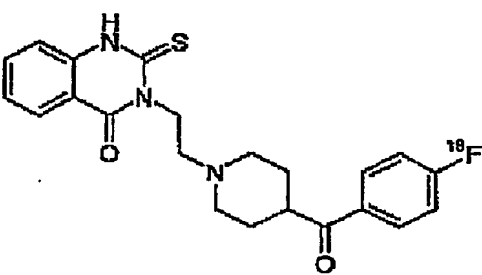
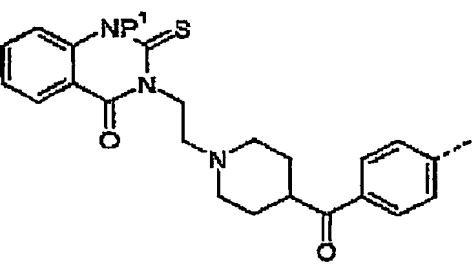
The precursor Q of Formulae I and II is preferably an aryl group optionally substituted by 1 to 5 substituents independently selected from nitro, cyano, halogen, C₁₋₁₀ hydroxyalkyl, C₂₋₁₀ carboxyalkyl, C₁₋₁₀ alkyl, C₂₋₁₀ alkoxyalkyl, C₁₋₁₀ hydroxyalkyl, C₁₋₁₀ aminoalkyl, C₁₋₁₀ haloalkyl, C₆₋₁₄ aryl, C₃₋₁₂ heteroaryl, C₃₋₂₀ alkylaryl, C₅₋₁₂ arylene, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ acyl, C₇₋₁₀ aroyl, C₂₋₁₀ carboalkoxy, C₂₋₁₀ carbamoyl, C₂₋₁₀ carbamyl, or C₁₋₁₀ alkylsulphinyl, or protected versions of any of these groups; or alternatively forms a four- to six-membered ring together with the R group to which it is adjacent, or protected versions thereof.

Especially preferred precursors Q are illustrated in Table I.

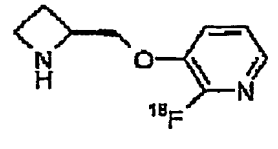
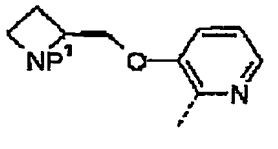
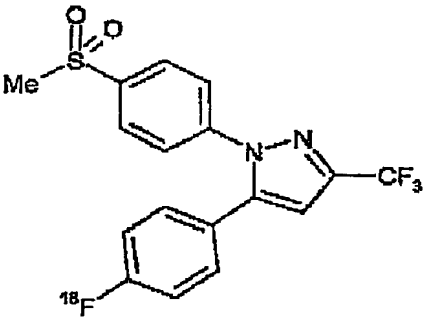
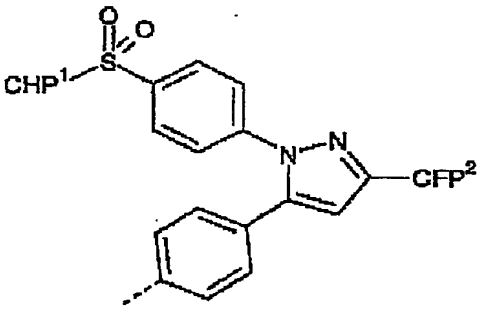
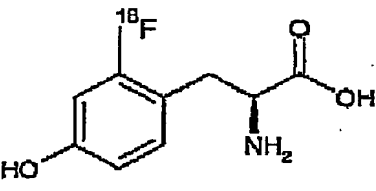
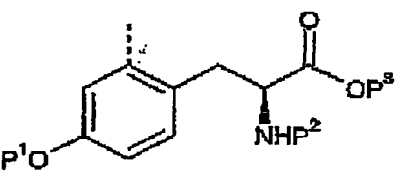
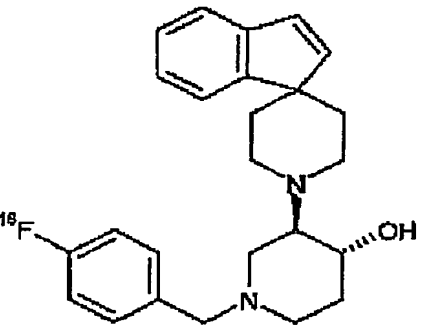
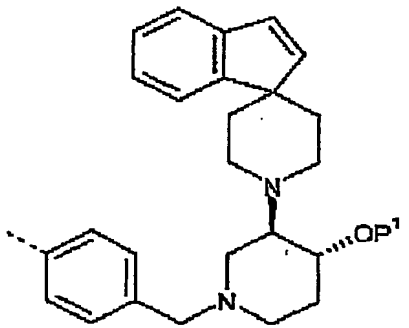
- 10 Whether the method of the invention is carried out in solution or on a solid phase, the fluorine-labelled compound of the invention is preferably an [¹⁸F]-labelled compound and the fluoride ion source is preferably a source of ¹⁸F⁻. Most preferably, the [¹⁸F]-labelled compound is an [¹⁸F]-labelled radiotracer, i.e. an [¹⁸F]-labelled compound that is suitable for the detection by PET imaging of particular biological targets within a subject.
- 15 The [¹⁸F]-labelled tracer is preferably selected from the compounds listed in the first column of Table I. The respective precursors of these [¹⁸F]-labelled tracers are given in the second column of Table I, wherein P¹-P⁴ are each independently hydrogen or a protecting group.

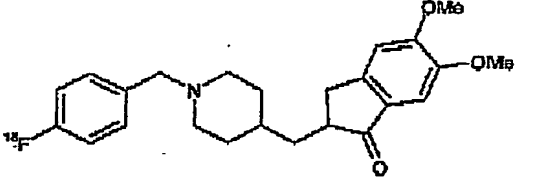
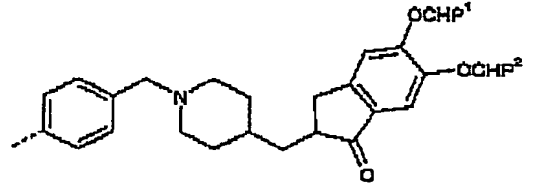
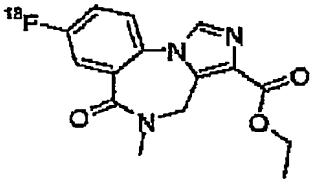
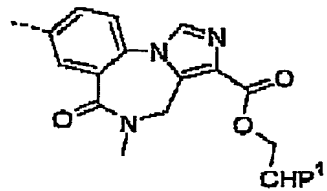
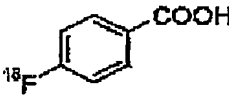
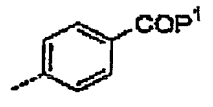
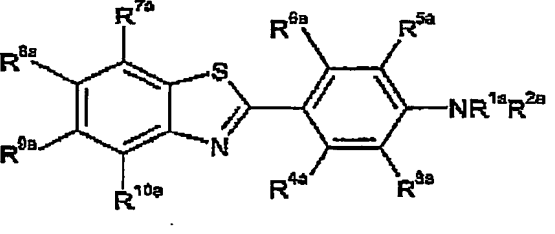
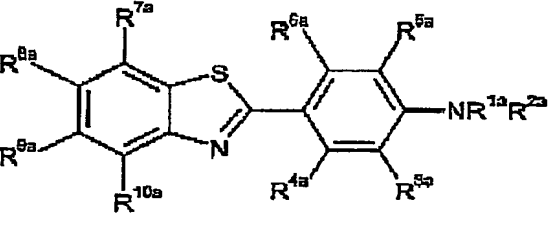
Table I

¹⁸ F Compound	Precursor (Q)
(a) [¹⁸ F]-FDOPA	
	
(b) [¹⁸ F]-dopamine	
	
(c) [¹⁸ F]-5-fluorouracil	
	
(d) [¹⁸ F]-mFBG	
	
(e) [¹⁸ F]-FIBG	

	
(f) [18F]-fluorocarazolol	
	
(g) [18F]-pmPPF	
	
(h) [18F]-altanaserine	
	
(i) [18F]-2-A85380	

8

	
(j) $[^{18}\text{F}]\text{-SC58125}$	
	
(k) $[^{18}\text{F}]\text{-Tyrosine}$	
	
(l) $[^{18}\text{F}]\text{-Spiro-FBT}$	
	
(m) $[^{18}\text{F}]\text{-FDP}$	

	
(n) [18F]-flumanezil	
	
(o) [18F]-SFB labelling agent	
	
(p) [18F]-Formula III*	
	

* for [18F]-Formula III: R^{1a} and R^{2a} are independently selected from hydrogen, a protecting group, C_{1-8} alkyl, C_{1-8} hydroxyalkyl, and C_{1-8} haloalkyl; one of R^{8a} to R^{10a} is a bond to the ^{18}F (in the case of the [18F]-compound) or one of R^{8a} to R^{10a} is a bond to the $-I^*$ group in formula (1a) (in the case of the precursor); and the other R groups are independently selected from hydrogen, halo, C_{1-8} alkyl, C_{1-8} haloalkyl, C_{1-8} hydroxyalkyl, C_{1-8} alkoxy, C_{1-8} haloalkoxy, cyano, and nitro.

Most preferred [^{18}F]-labelled compounds of the invention are [^{18}F]-DOPA, [^{18}F]-dopamine, and [^{18}F]-fluorouracil, with [^{18}F]-DOPA being especially preferred.

In a second aspect the present invention relates to an [^{18}F]-labelled compound produced by the method of the invention.

5 Brief Description of the Examples

Example 1 describes a known method of radiofluoridation of diphenyliodonium triflate which produced highly variable yields.

Example 2 describes the method of Example 1 carried out in the presence of 50 mole% TEMPO. The radiochemical yields obtained were considerably more consistent than those obtained in the absence of a radical scavenger suggesting that the variability observed with the method of Example 1 was at least partly as a result of the presence of free radicals.

Example 3 describes the method of Example 1 carried out in the presence of 50 mole% 1,2-diphenylethylene (1,2-DPE). The radiochemical yield was similar to that obtained with TEMPO demonstrating that alternative radical traps may also be used.

Examples 4-8 describe the radiofluoridation of a variety of other iodonium salts in the presence of 50 mole% TEMPO. A radiochemical yield similar to that obtained in Example 2 for radiofluoridation of diphenyliodonium triflate in the presence of TEMPO was obtained demonstrating that other iodonium salts can be radiofluoridated by the method of the invention.

Example 5 describes how the radiofluoridation reaction would be carried out in the case of iodonium salts immobilised onto a solid phase. As has been demonstrated with the solution phase method, it is anticipated that consistent radiochemical yields would also be obtained with this method.

Examples 6-9 describe the preparation of various solid-phase bound iodonium salts that may be fluoridated or radiofluoridated by the methods of the invention.

Examples***Comparative Example 1: Radiofluoridation of diphenyliodonium triflate in the absence of radical scavenger***

[¹⁸F] Fluoride in ¹⁸O enriched water (~0.3ml) was loaded into a reaction vessel, to this
5 was added kryptofix 222 (11.4 mg) and potassium carbonate (0.2 ml of a 0.1 M solution)
in acetonitrile. The fluoride was dried by azeotropic drying. Following the completion of
the drying process, a solution of diphenyliodonium triflate (ex Sigma-Aldrich Chemicals,
22.5 mg) in dry acetonitrile (1 ml) was added to the dry fluoride. The mixture was
heated at 95°C for 15 minutes before being cooled in a stream of compressed air. The
10 product was transferred to a sealed collection vial and the reaction analysed by HPLC.

Radiochemical purity (RCP) and RCY values obtained are presented in the table below:

Reaction No	RCP	RCY
1	0	0
2	10	5
3	64	24
4	50	28
5	5	4
6	41	30
7	9	5
8	60	40
9	15	11
10	4	3
11	6	4
12	4	3
13	0	0
14	3	2
15	3	3
16	0	0
17	18	10
18	7	4
19	22	1
20	23	18
21	49	23
22	22	9

Example 2: Radiofluoridation of diphenyliodonium triflate in the presence of 50 mole% TEMPO

The same reaction as described in Example 1 was carried out in the presence of 50 Mol% TEMPO.

- 5 The RCP and RCY values obtained are presented in the table below:

Reaction No	RCP	RCY
28	96	45
29	94	57
30	95	45
31	91	70
32	97	47
33	97	41
34	82	49

Example 3: Radiofluoridation of diphenyliodonium triflate in the presence of 50 mol% 1,2-DPE

The same reaction as described in Example 1 was carried out in the presence of 50 Mol% of 1,2-DPE.

- 10 The RCP and RCY values obtained are presented in the table below:

Reaction No	RCP	RCY
35	64	37

Example 4: Radiofluoridation of (2-methyl-4-methoxyphenyl)phenyliodonium trifluoroacetate in the presence of 50 mol% TEMPO

- 15 [¹⁸F]-fluoride in ¹⁸O enriched water (~0.4ml) was loaded into the reaction vessel, to this was added a mixture of a solution of Kryptofix (17.9 mg, ex Sigma-Aldrich Chemicals) in acetonitrile (1ml) and potassium carbonate (0.2 ml of a 0.1 M aqueous solution). The fluoride was dried by azeotropic drying. Following the completion of the drying process, a solution of (2-methyl 4-methoxyphenyl)phenyliodonium trifluoroacetate (21.2 mg) and TEMPO (ex Sigma-Aldrich Chemicals) (7.8 mg) in acetonitrile (1 ml) was added to the dry fluoride. The mixture was heated at 95°C for 15 minutes before being cooled in a

stream of compressed air. The product was transferred to a sealed collection vial and the reaction analysed by HPLC.

The RCP and RCY values obtained are presented in the table below:

Reaction No	RCP	RCY
36	85	52
37	63	45

5 ***Example 5: Radiofluoridation of 2-Methoxyphenyl 4'methoxy-2'methyliodonium trifluoroacetate in the presence of 50 mol% TEMPO***

The method used was as described above in Example 4 except that 2-Methoxyphenyl 4'methoxy-2'methyliodonium trifluoroacetate was used in place of (2-methyl-4-methoxyphenyl)phenyliodonium trifluoroacetate.

The RCP and RCY values obtained are presented in the table below:

Reaction No	RCP	RCY
38	58	28
39	88	59

10 ***Example 6: Radiofluoridation of 2-Methoxyphenyl 5'-benzoyloxy-4-methoxy-2-methyl trifluoroacetate in the presence of 50 mol% TEMPO***

The method used was as described above in Example 4 except that 2-Methoxyphenyl 5'-benzoyloxy-4-methoxy-2-methyl trifluoroacetate was used in place of (2-methyl-4-methoxyphenyl)phenyliodonium trifluoroacetate.

Reaction No	RCP	RCY
40	25	17
41	70	28

15 ***Example 7: Radiofluoridation of Phenyl 5-benzoyloxy—4-methoxy-2-methyliodonium trifluoroacetate in the presence of 50 mol% TEMPO***

The method used was as described above in Example 4 except that Phenyl 5-benzoyloxy—4-methoxy-2-methyliodonium trifluoroacetate was used in place of (2-methyl-4-methoxyphenyl)phenyliodonium trifluoroacetate.

Reaction No	RCP	RCY
42	86	50

Example 8: Radiofluoridation of (1-methoxypyrazole)(2-methoxyphenyl)iodonium trifluoroacetate in the presence of 50 mol% TEMPO

The method used was as described above in Example 4 except that (1-methoxypyrazole)(2-methoxyphenyl)iodonium trifluoroacetate was used in place of (2-methyl-4-methoxyphenyl)phenyliodonium trifluoroacetate.

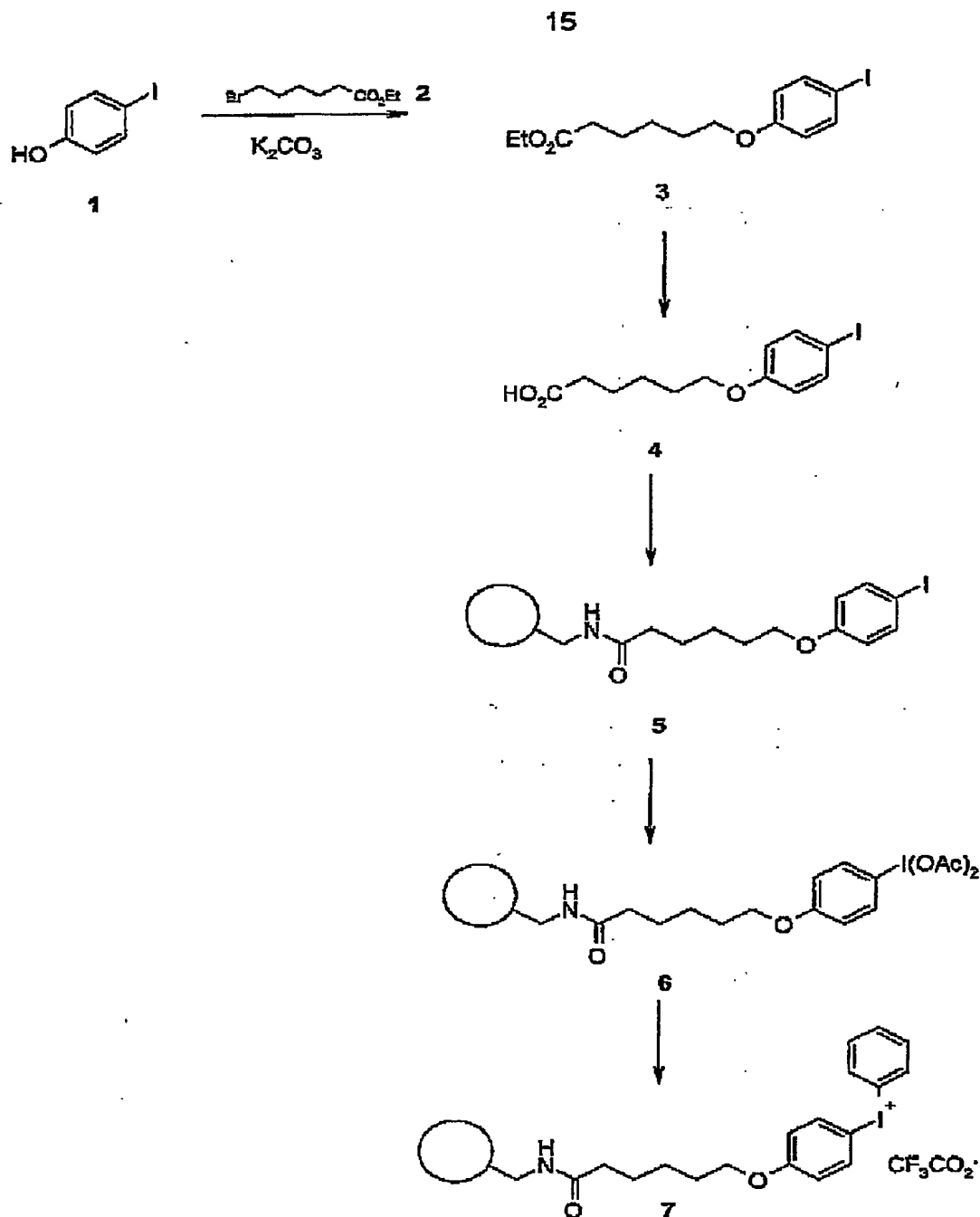
Reaction No	RCP	RCY
43	81	61

Example 9: Radiofluoridation of resin bound iodonium salt in the presence of 50 mol% TEMPO

TEMPO (ex Sigma-Aldrich Chemicals) (7.8 mg) in acetonitrile (0.5 ml) is added to the iodonium resin (98.3 mg) and then heated to 100°C and then allowed to cool to ambient temperature. [¹⁸F]-fluoride in ¹⁸O enriched water (~0.4ml) is loaded into a separate reaction vessel, to this is added a mixture of a solution of Kryptofix (17.9 mg, ex Sigma-Aldrich Chemicals) in acetonitrile (1ml) and potassium carbonate (0.2 ml of a 0.1 M aqueous solution). The fluoride is dried by azeotropic drying. Following the completion of the drying process, TEMPO (9.6 mg) in dry acetonitrile (1.5 ml) is added and the mixture heated to 80°C for ten minutes, then cooled by a stream of compressed air. The solution is then added to the resin and the reaction heated at 80°C for 10 minutes. The vessel is cooled to 30°C and the product transferred into a product vial. The reaction is analysed by HPLC.

Example 10: Preparation of 6-(4-phenyliodoniumphenoxy)hexanoic acid - amino methyl polystyrene amide trifluoroacetate salt

The synthetic route is illustrated below:



(a) Preparation of ethyl 6-(4-iodophenoxy)hexanoate (3)

Ethyl 6-bromohexanoate (5.55g, 25mmol) in acetone (100ml) was treated with 4-iodophenol (5.55g, 25mmol) and potassium carbonate (6.9g 50mmol). The stirred reaction was heated under reflux for 60h. The reaction was then allowed to cool and the reaction concentrated in vacuum to a gum. The reaction was then partitioned

between ethyl acetate (100ml) and water (100ml). The ethyl acetate layer was separated dried, over magnesium sulfate and concentrated *in vacuo* to give a colourless gum (8.71 g, 24.1 mmol, 96%), δ_H ($CDCl_3$) 1.26 (3H, t, $CO_2CH_2CH_3$), 1.46 – 1.81 (6H, m, 3,4,5- CH_2), 2.33 (2H, t, 2- CH_2), 3.91 (2H, t, 6- CH_2), 4.13 (2H, q, $CO_2CH_2CH_3$), 6.68 (2H, dd, 2,6-ArH), 7.53 (2H, dd, 3,5-ArH), δ_H ($CDCl_3$) 14.20, 24.60, 25.53, 28.75, 34.14, 60.20, 67.67, 82.44, 116.83, 138.09, 158.84, and 173.52.

(b) Preparation of 6-(4-iodophenoxy)hexanoic acid (4)

Ethyl 6-(4-iodophenoxy)hexanoate (3.62g, 10mmol), in ethanol (30ml), water (30ml) was treated with sodium hydroxide (1g, 25mmol) and the reaction was stirred under reflux for 3h. The reaction was then allowed to cool and concentrated in vacuum to a solid. The solid was then treated cautiously with ethyl acetate (100ml) and 1N hydrochloric acid (100ml) and the reaction stirred at room temperature for 10 min. The ethyl acetate layer was separated dried over sodium sulfate and concentrated in vacuum to give a pale yellow solid (3.11g, 9.3 mmol, 93%), δ_H ($CDCl_3$) 1.48 – 1.82 (6H, m, 3,4,5- CH_2), 2.40 (2H, t, 2- CH_2), 3.91 (2H, t, 6- CH_2O), 6.67 (2H, dd, 2,6-ArH), 7.53 (2H, dd, 3,5-ArH), δ_D ($CDCl_3$) 24.31, 25.50, 38.75, 33.89, 82.54, 116.87, 138.14, 158.83 and 179.97

(c) Preparation of 6-(4-iodophenoxy)hexanoic acid - aminomethyl polystyrene resin amide (5)

Aminomethyl polystyrene resin (4.28g, 6mmol) in dichloromethane (30ml) was treated with 6-(4-iodophenoxy)hexanoic acid (2.672g, 8mmol), diisopropylethylamine (2.322g 18mmol) and diphenylphosphoryl chloride (1.888g, 8mmol). The reaction was placed on a blood wheel and kept under agitation for 18h. The reaction was then filtered and the resin washed with dichloromethane (100ml). The resin was then dried in vacuum to give the desired aryl iodide substituted resin (6.3039g). Found C 75.36%, H 6.62%, N 1.52%, I 11.12%

(d) Oxidation of 6-(4-iodophenoxy)hexanoic acid - aminomethyl polystyrene resin amide with peracetic acid (6)

6-(4-iodophenoxy)hexanoic acid - aminomethyl polystyrene resin (1g, 1mmol) in dichloromethane (15ml) was treated with peracetic acid (5ml). The reaction was stirred with an overhead stirrer for 18h at room temperature. The reaction was then filtered and

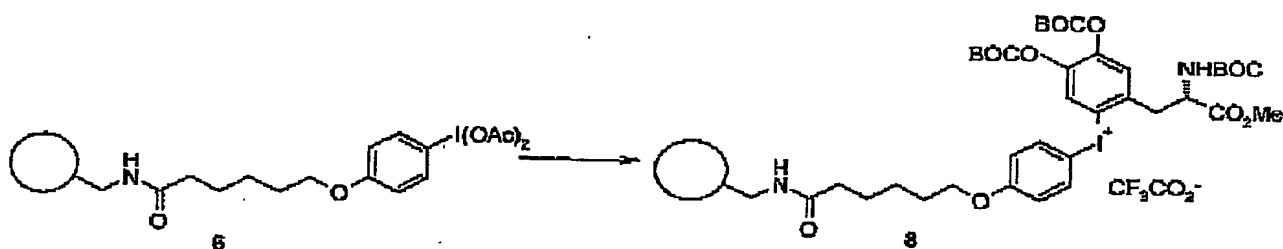
the resin washed with dichloromethane (100ml). The resin was then dried in vacuum to give a yellow solid.

(e) Reaction of 6-(4-diacetoxyiodophenoxy)hexanoic acid - aminomethyl polystyrene amide with tri-*n*-butylphenyltin and trifluoroacetic acid to give 6-(4-phenyliodoniumphenoxy)hexanoic acid - amino methyl polystyrene amide trifluoroacetate salt (resin bound iodonium salt 1) (7)

6-(4-diacetoxyiodophenoxy)hexanoic acid - aminomethyl polystyrene amide (1g, 0.5mmol), in dichloromethane (10ml) was cooled to -40C was treated with tri-*n*-butyl phenyl tin (367mg, 1mmol). The stirred reaction was then treated with trifluoroacetic acid (288mg 2.0mmole) and allowed to warm to room temperature over 2h. The resin was washed thoroughly with dichloromethane. Found: C 70.47%, H 5.81%, N 1.53%, I 11.59%, F 3.78% δ_F (CDCl₃) - 78.

Example 11: Preparation of 6-(2-((*S*)-3-methoxycarbonyl-3-*N*-*t*-butoxycarbonyl-4,5-di(*t*-butoxycarbonyloxy)phen-6-yl)phenoxy)hexanoic acid - amino methyl polystyrene amide trifluoroacetate salt

The synthetic route is illustrated below:

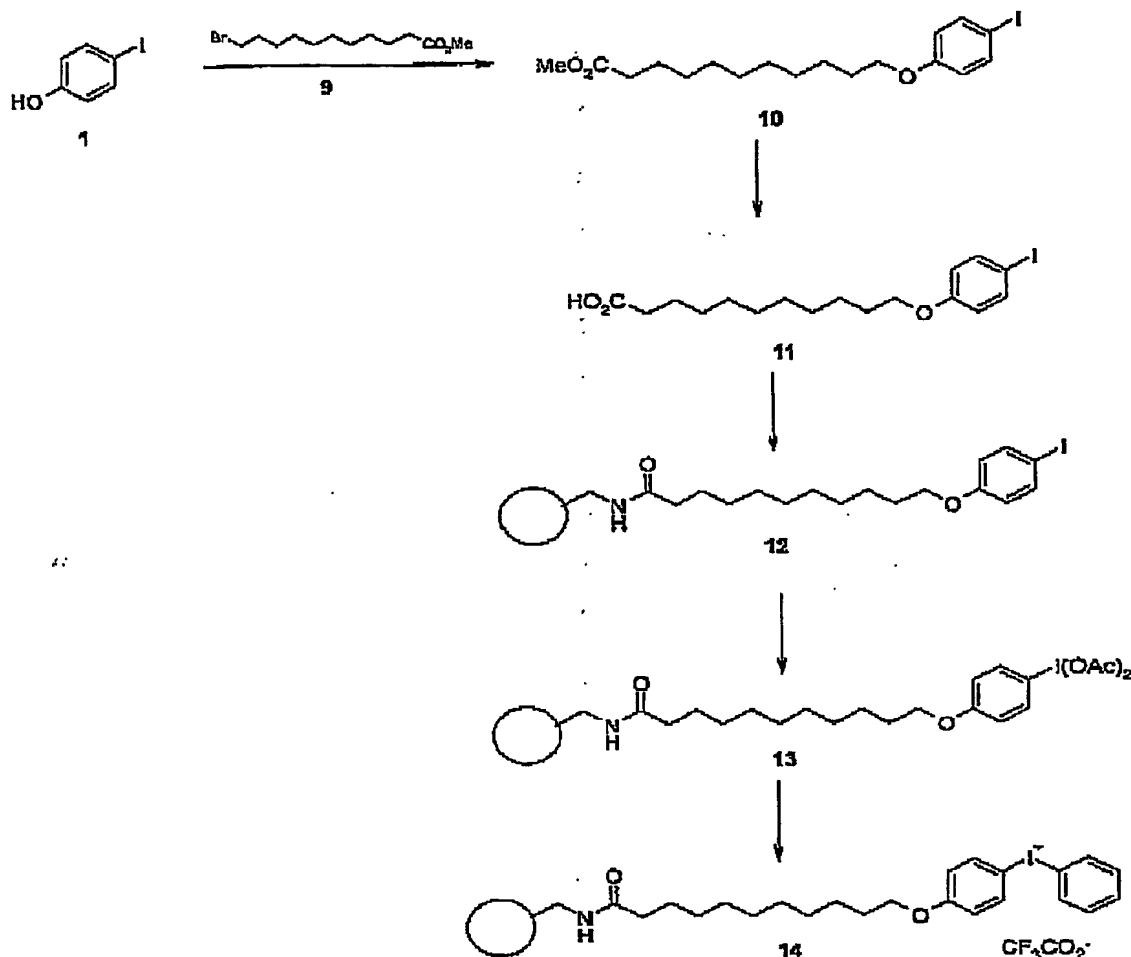


6-(4-diacetoxyiodophenoxy)hexanoic acid - aminomethyl polystyrene amide, in dichloromethane is cooled to -40C is treated with methyl *N*-*t*-butoxycarbonyl-3,4-di(*t*-butoxycarbonyloxy)-6-trimethylstannylphenylalanine. The stirred reaction is then treated with trifluoroacetic acid and allowed to warm to room temperature over 2h. The resin is washed thoroughly with dichloromethane

18

Example 12: Preparation of 6-(4-phenyliodonium-phenoxy)undecanoic acid - aminomethyl polystyrene amide trifluoroacetate salt

The synthetic route is illustrated below:



5 (a) Preparation of methyl 11-(4-iodophenoxy)undecanoate (10)

Methyl 11-bromoundecanoate (10g, 35.8mmol), in acetone (150ml) was treated with 4-iodophenol (7.88g, 35.8mmol) and potassium carbonate (9.88g 71.6mmol). The stirred reaction was heated at reflux for 48h. The reaction was then allowed to cool and the reaction concentrated *in vacuo* to a gum. The reaction was then partitioned between ethyl acetate (150ml) and water (150ml). The ethyl acetate layer was separated dried, over sodium sulfate and concentrated *in vacuo* to solid. The solid was dissolved in diethyl ether (100ml) and petroleum ether 60-80C (100ml) added. The solution was

concentrated in vacuum to a volume of 100ml. The solution was set aside and allowed to crystallise. The product was collected by filtration and dried in vacuum to give 12.22g of solid. The mother liquors were concentrated to ~20ml and allowed to crystallise. A further 0.81g of solid was collected by filtration. The two solids were combined to give the desired product (13.03 g, 86%) δ_H (CDCl₃) 1.29 – 1.78 (16H, m, 3,4,5,6,7,8,9,10-CH₂), 2.30 (2H, t, 2-CH₂), 3.86 (3H, s, CO₂CH₃), 3.90 (2H, t, 11-CH₂), 6.66 (2H, dd, 2,6-ArH), 7.53 (2H, dd, 3,5-ArH). δ_C (CDCl₃) 24.90, 25.93, 29.09, 29.18, 29.30, 29.42, 34.07, 51.42, 68.06, 82.35, 116.90, 138.11, 158.98, and 174.33.

10 (b) Hydrolysis of methyl 11-(4-iodophenoxy)undecanoate (11)

Methyl 11-(4-iodophenoxy)undecanoate (10g, 23.9mmol), in methanol (100ml) was treated with sodium hydroxide (2.4g, 60mmol). The stirred reaction was heated at 40C for 60h. The reaction contained a heavy white precipitate at the end of the reaction. The reaction was then cooled to room temperature and concentrated *in vacuo*. The resulting solid was then treated with 1N hydrochloric acid (250ml) and ethyl acetate (250ml) and stirred vigorously until the solid had dissolved. The organic phase was separated dried over sodium sulfate and concentrated *in vacuo* to give 11-(4-iodophenoxy)-undecanoic acid (9.55 g, 23.6 mmol, 98 %) δ_H (CDCl₃) 1.29 – 1.78 (16H, m, 3,4,5,6,7,8,9,10-CH₂), 2.35 (2H, t, 2-CH₂), 3.90 (2H, t, 11-CH₂), 6.66 (2H, dd, 2,6-ArH), 7.53 (2H, dd, 3,5-ArH). δ_C (CDCl₃) 24.61, 25.92, 28.98, 29.08, 29.16, 29.27, 29.41, 34.02, 68.08, 82.37, 116.90, 138.11, 158.97, and 180.18.

(c) Preparation of 11-(4-iodophenoxy)undecanoic acid - aminomethyl polystyrene resin amide (12)

Aminomethyl polystyrene resin (4.28g, 6mmol) in dichloromethane (30ml) was treated with 11-(4-iodophenoxy)undecanoic acid (3.12g, 8mmol), diisopropylethylamine (2.32g, 18mmol) and diphenylphosphoryl chloride (1.89g, 8mmol). The reaction was placed on a blood wheel and kept under agitation for 18h. The reaction was then filtered and the resin washed with dichloromethane (100ml). The resin was then dried *in vacuo* to give the desired aryl iodide substituted resin (6.30g).

(d) Oxidation of 11-(4-iodophenoxy)undecanoic acid - amino methyl polystyrene resin amide with peracetic acid (13)

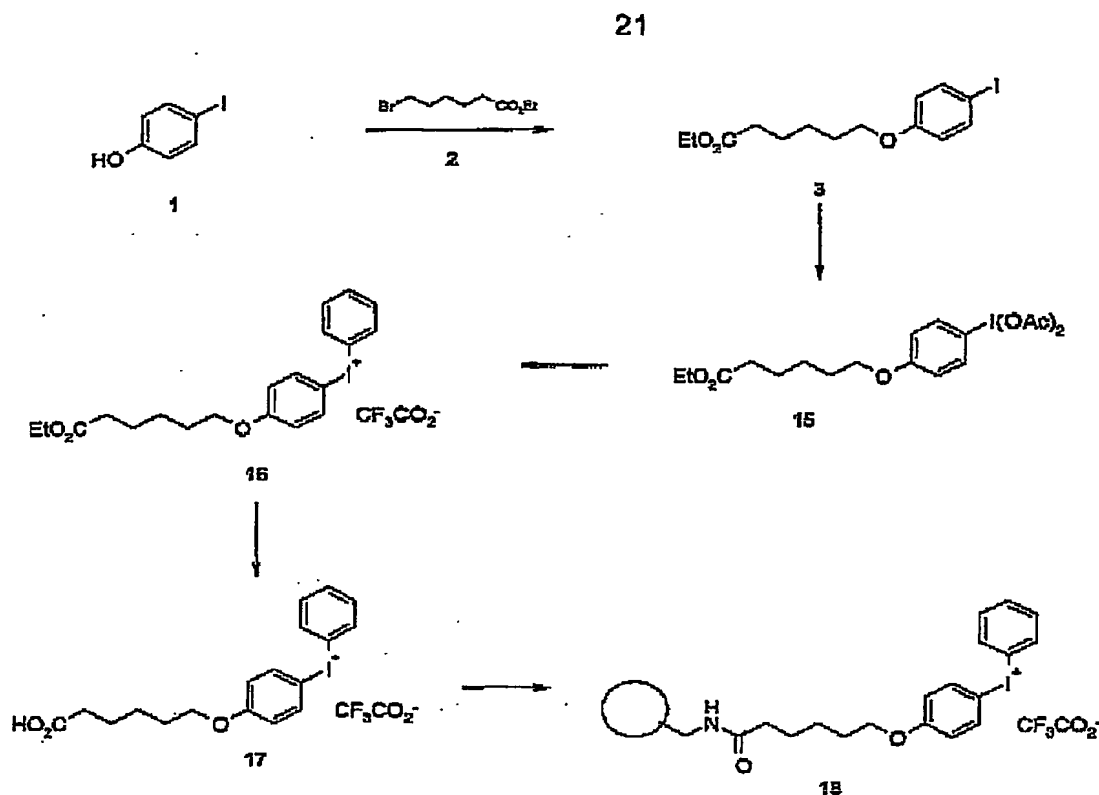
11-(4-iodophenoxy)undecanoic acid - amino polystyrene resin (1g, 1mmol) in dichloromethane (15ml) was treated with peracetic acid (5ml). The reaction was stirred with an overhead stirrer for 18h at room temperature. The reaction was then filtered and the resin washed with dichloromethane (500ml). The resin was then dried in vacuum to give a yellow solid (990mg).

(e) Reaction of 6-(4-diacetoxyiodo-phenoxy)undecanoic acid - aminomethyl polystyrene amide with tri-*n*-butylphenyltin and trifluoroacetic acid to give 6-(4-phenyliodonium-phenoxy)undecanoic acid - aminomethyl polystyrene amide trifluoroacetate salt (14)

6-(4-diacetoxyiodophenoxy)undecanoic acid - aminomethyl polystyrene amide in dichloromethane is cooled to -40C is treated with tri-*n*-butylphenyltin. The stirred reaction is then treated with trifluoroacetic acid and allowed to warm to room temperature over 2h. The resin is washed thoroughly with dichloromethane.

Example 13: Preparation of 6-(4-(phenyliodonium)phenoxy)hexanoic acid - aminomethyl amide polystyrene trifluoroacetate salt

The synthetic route is illustrated below:



(a) Peracetic acid oxidation of ethyl 6-(4-iodophenoxy)hexanoate (15)

Ethyl 6-(4-iodophenoxy)hexanoate (3.62g, 10mmol) was treated with peracetic acid (39%) (5ml) and dichloromethane (15ml) on an ice bath with stirring. The reaction was allowed to warm to room temperature whilst stirred over a period of 2h. The reaction initially darkened but after 30 min became a pale yellow colour. The reaction was then partitioned between dichloromethane (30ml) and water (30ml). The dichloromethane layer was separated dried over magnesium sulfate and concentrated under high vacuum to a gum (4.53g, 9.4 mmol, 94%) δ_H (CDCl₃) 1.26 (3H, t, CO₂CH₂CH₃), 1.51 - 1.85 (6H, m, 3,4,5-CH₂), 2.00 (6H, s, 2 x CH₃CO₂), 2.34 (2H, t, 2-CH₂), 4.01 (2H, t, 6-CH₂), 4.14 (2H, q, CO₂CH₂CH₃), 6.94 (2H, dd, 2,6-ArH), 8.00 (2H, dd, 3,5-ArH); δ_C (CDCl₃) 14.18, 20.31, 24.52, 25.47, 28.61, 34.10, 60.24, 68.27, 111.34, 116.98, 137.07, 161.63, 173.67, and 176.32.

(b) Reaction of ethyl 6-(4-diacetoxyiodophenoxy)hexanoate with tri-*n*-butylphenyltin

(16)

Ethyl 6-(4-diacetoxyiodophenoxy)hexanoate (905mg, 2.5mmol) in dichloromethane (10ml) was cooled to -40C and treated with tri-*n*-butylphenyltin (954mg, 2.6mmole) and

trifluoroacetic acid (592mg, 5.2mmole). The reaction was stirred for 1h whilst it was allowed to warm to room temperature. The reaction was concentrated under high vacuum to give a gum (2.4 g) containing product and tri-*n*-butyltrifluoroacetate.

(c) Hydrolysis of ethyl 6-(4-phenyl iodonium phenoxy)hexanoate trifluoroacetate salt with aqueous trifluoroacetic acid (17)

Ethyl 6-(4-phenyliodoniumphenoxy)hexanoate (350mg, 0.729mmol) in water/trifluoroacetic acid 1:1 (10ml) was stirred for 18h at 80C. The reaction was then concentrated in high vacuum to give the products as a gum. The gum was stirred with petroleum ether and the iodonium salt was freed of the solution of the tri-*n*-butyltin trifluoroacetate from the previous step by decanting off the supernatant solution.

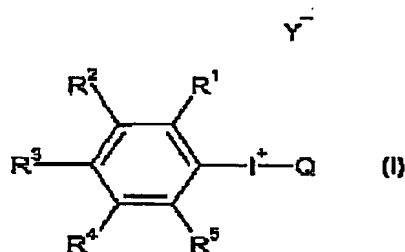
(d) Coupling of 6-(4-(phenyliodonium)phenoxy)hexanoic acid trifluoroacetate salt with aminomethyl polystyrene resin (18)

To aminomethyl polystyrene resin (714mg) in dichloromethane (15ml) was added crude 6-(4-(phenyliodonium)phenoxy)hexanoic acid trifluoroacetate salt (1.2g, 1.25mmol) diphenylphosphinic chloride (295mg, 1.25mmole) and diisopropylethylamine (387mg, 3.0mmole). The reaction was shaken on a blood wheel overnight and then washed with methanol/dichloromethane (100ml) followed by dichloromethane (100ml). The resin was then dried *in vacuo* to give the resin as a solid (0.95 g).

Found: C 72.85%, H 62.6%, N 1.53%, I 7.49%, F 1.67%.

Claims

- 1) A method for the production of an aromatic fluorine-labelled compound comprising fluoridation of an iodonium salt with a fluoride ion source characterised in that the reaction mixture contains a free radical trap.
- 2) The method of claim 1 wherein the free radical trap is selected from 2,2,6,6-Tetramethylpiperidine-N-Oxyl, ascorbate, para-amino benzoic acid, α -tocopherol, hydroquinone, di-t-butyl phenol, β -carotene and gentisic acid.
- 3) The method of either of claims 1 or 2 wherein the free radical trap is 2,2,6,6-Tetramethylpiperidine-N-Oxyl.
- 4) The method of any of claims 1-3 wherein the fluoride ion source is selected from potassium fluoride, caesium fluoride and tetraalkylammonium fluoride.
- 5) The method of claim 4 wherein the fluoride ion source is potassium fluoride and KryptofixTM is used to activate the fluoride ion.
- 6) The method of any of claims 1-5 wherein the iodonium salt is of Formula I:



wherein:

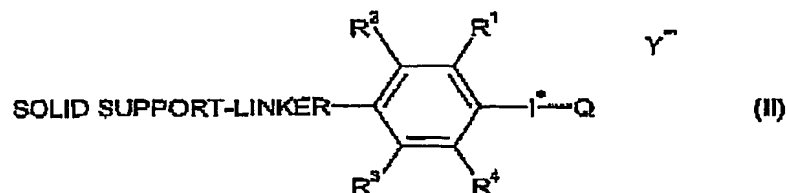
Q is a precursor of the fluorine-labelled compound of the invention;

R¹-R⁵ are independently selected from hydrogen, nitro, cyano, halogen, C₁₋₁₀ hydroxyalkyl, C₂₋₁₀ carboxyalkyl, C₁₋₁₀ alkyl, C₂₋₁₀ alkoxyalkyl, C₁₋₁₀ hydroxyalkyl, C₁₋₁₀ aminoalkyl, C₁₋₁₀ haloalkyl, C₆₋₁₄ aryl, C₃₋₁₂ heteroaryl, C₃₋₂₀ alkylaryl, C₅₋₁₂ arylene, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, C₁₋₁₀ acyl, C₇₋₁₀ aroyl, C₂₋₁₀ carboalkoxy, C₂₋₁₀ carbamoyl, C₂₋₁₀ carbamyl, or C₁₋₁₀ alkylsulphinyl, or protected versions of any of

these groups; or alternatively forms a four- to six-membered ring together with the R group to which it is adjacent, or protected versions thereof; and,

Y^- is an anion selected from triflate, nonaflate, mesylate and hexaflate.

- 7) The method of any of claims 1-5 wherein the iodonium salt is solid support-bound as in Formula II:



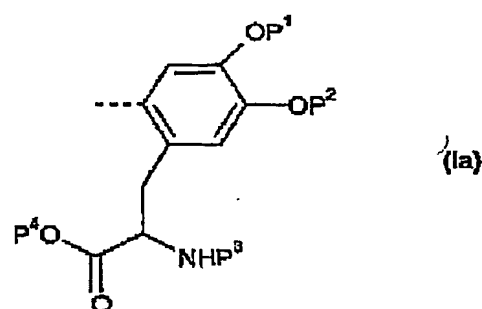
wherein:

Q is a precursor of the fluorine-labelled compound; and,

R^1 - R^4 and Y^- are as defined for Formula I of claim 6.

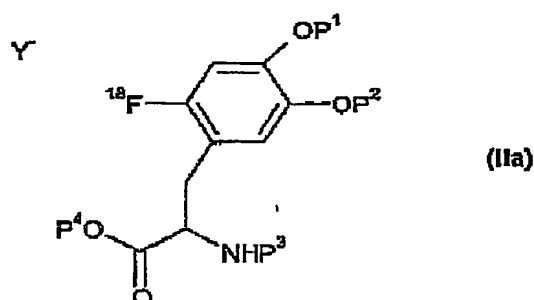
- 8) The method of either of claims 6 or 7 wherein Q is an aryl group optionally substituted by 1 to 5 substituents independently selected from nitro, cyano, halogen, C_{1-10} hydroxyalkyl, C_{2-10} carboxyalkyl, C_{1-10} alkyl, C_{2-10} alkoxyalkyl, C_{1-10} hydroxyalkyl, C_{1-10} aminoalkyl, C_{1-10} haloalkyl, C_{6-14} aryl, C_{3-12} heteroaryl, C_{3-20} alkylaryl, C_{5-12} arylene, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{1-10} acyl, C_{7-10} aroyl, C_{2-10} carboalkoxy, C_{2-10} carbamoyl, C_{2-10} carbamyl, or C_{1-10} alkylsulphanyl, or protected versions of any of these groups; or alternatively forms a four- to six-membered ring together with the R group to which it is adjacent, or protected versions thereof.
- 9) The method of any of claims 1-8 wherein the fluorine-labelled compound is an $[^{18}F]$ -labelled compound and the fluoride ion source is a source of $^{18}F^-$.
- 10) The method of claim 9 wherein the $[^{18}F]$ -labelled compound is $[^{18}F]$ -FDOPA.
- 11) The method of any of claims 6-10 wherein the precursor is of Formula Ia:

25



wherein P^1 , P^2 , P^3 , and P^4 are each independently hydrogen or a protecting group;

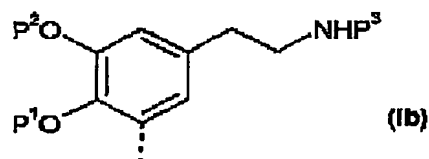
said method producing the labelled compound of Formula IIa:



5 wherein P^1 , P^2 , P^3 , and P^4 are each independently hydrogen or a protecting group and Y^- is an anion, preferably trifluoromethylsulphonate (triflate) anion.

12) The method of claim 9 wherein the [^{18}F]-labelled compound is [^{18}F]-dopamine.

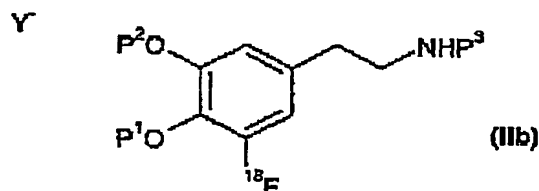
13) The method of any of claims 6-10 and 12 wherein the precursor is of Formula Ib:



10 wherein P^1 , P^2 , and P^3 are each independently hydrogen or a protecting group;

said method producing the labelled compound of Formula IIb:

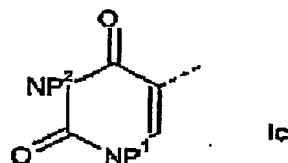
26



wherein P^1 , P^2 , and P^3 are each independently hydrogen or a protecting group and Y^- is an anion, preferably trifluoromethylsulphonate (triflate) anion.

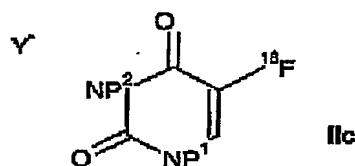
14) The method of claim 9 wherein the $[^{18}F]$ -labelled compound is $[^{18}F]$ -uracil.

5 15) The method of any of claims 6-10 and 14 wherein the precursor is of Formula Ic:



wherein P^1 and P^2 are each independently hydrogen or a protecting group;

said method producing the labelled compound of Formula IIc:



10 wherein P^1 and P^2 are each independently hydrogen or a protecting group and Y^- is an anion, preferably trifluoromethylsulphonate (triflate) anion.

16) The method of any of claims 9-15, further comprising:

(i) removal of excess $^{18}F^-$, for example by ion-exchange chromatography; and/or

15 (ii) removal of the protecting groups; and/or

(iii) removal of organic solvent; and/or

(iv) formulation of the resultant compound as an aqueous solution.

E

27

17) An [^{18}F]-labelled compound produced by the method of any of claims 1-16.

Abstract

Decomposition of Iodonium salts by a free radical process has been identified as a significant factor in the observed yield variability of fluorination reactions using said Iodonium salts. Accordingly, the inclusion of a free radical trap in the reaction mixture
5 blocks the radical chain decomposition pathway for Iodonium salts such that only the reaction leading to fluorination can occur and the yield of aryl fluoride becomes high and reproducible. The reaction may also be carried out on solid phase. In both the solution and the solid phase the preferred method of the present invention is radiofluorination.

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/GB04/005304

International filing date: 17 December 2004 (17.12.2004)

Document type: Certified copy of priority document

Document details: Country/Office: GB
Number: 0329716.5
Filing date: 23 December 2003 (23.12.2003)

Date of receipt at the International Bureau: 24 January 2005 (24.01.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

☐ **BLACK BORDERS**

☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**

☐ **FADED TEXT OR DRAWING**

☒ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**

☐ **SKEWED/SLANTED IMAGES**

☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**

☐ **GRAY SCALE DOCUMENTS**

☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**

☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**

☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.